DuPont Pharmaceuticals Company

August 29, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Reference: Docket No. 00D-1407

VIA FEDERAL EXPRESS

Dear Sir or Madam:

In reference to Docket No. 00D-1407, attached are comments on the guidance document "S7 Safety Pharmacology Studies for Human Pharmaceuticals".

Please contact me at (302) 892-0694 or by facsimile (302) 892-0712 if you have any questions.

Sincerely,

Robert W Baluta for

Thomas E. Donnelly, Jr. Ph.D.
Executive Director, Regulatory Affairs

Attachments

00D-1407

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Chestnut Run Plaza • 974 Centre Road • Wilmington, DE 19805 • (302) 992-5000

Attachment 1

COMMENTS ON GUIDANCE DOCUMENT

S7 SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

DUPONT PHARMACEUTICALS COMPANY

Definitions of Safety Pharmacology Studies (Section 1.5), Safety Pharmacology Core Battery (Section 2.7) and Their Impact on Need for GLP (Section 2.11)

Although it is appropriate to clearly define the three categories of pharmacology studies, the definitions in the guideline are not distinct and are used inconsistently. This is likely to result in some confusion in their interpretation by various pharmaceutical sponsors. The distinction between Secondary Pharmacodynamic Studies and Safety Pharmacology Studies is a major cause of concern. In Note 2, Secondary Pharmacodynamic Studies are "Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target". These effects may of course be desirable or undesirable. In Section 1.5, Safety Pharmacology Studies are: "Those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relationship to exposure." By these definitions, it is reasonable to expect that Secondary Pharmacodynamic Studies would come before Safety Pharmacology Studies to determine what other effects may occur and be "potentially undesirable". Commonly Secondary Pharmacodynamic Studies consist of a screen of the effects of the drug on vital functions not associated with the drug's desired therapeutic effect. However, this guidance document refers to these Secondary Pharmacodynamic Studies as the Safety Pharmacology Core Battery (Section 2.7). The Core Battery should more correctly be termed the "Secondary Pharmacodynamics Core Battery."

It would be more accurate and consistent to define Safety Pharmacology Studies as "those studies that are appropriate to further investigate the potentially undesirable effects identified in the Secondary Pharmacodynamics Core Battery".

Section 2.11 refers to the Application of Good Laboratory Practice and is poorly written, as it is difficult to determine when GLP should be used. The basic problem is the inappropriate definition of Safety Pharmacology Studies vs. Secondary Pharmacodynamic Studies. For example, the fourth paragraph refers to Secondary Pharmacodynamic Studies and states that they "do not need to be conducted according to GLP, where their objectives differ from safety pharmacology studies." The second paragraph states that "The Safety Pharmacology Core Battery is normally conducted under GLP". However the last paragraph of the section contradicts this and states that "Safety pharmacology studies conducted as general screens in the absence of specific cause for concern do not need to be conducted according to GLP". Since the Core Battery is done in the absence of specific cause, this also justifies renaming the Core Battery the "Secondary Pharmacodynamics Core Battery", which as stated would not be done under GLP. The document should then state that follow-up Safety Pharmacology studies are normally

conducted under GLP and also include the comments on what should be done in lieu of formal GLP.

Another point of confusion among sponsors is the situation where the secondary pharmacodynamic studies and safety pharmacology studies are done early in development by the Pharmacology Department and would not be done under GLP. Other sponsors may choose to do these studies later in development and they would normally then be done in the Toxicology Department and under GLP. The document comes down rather forcefully on the use of GLP. It should be stressed that a study not done under GLP can still be scientifically valid.

Section 2.6 Studies on Metabolites, Isomers and Finished Products

The issue of human metabolites being tested separately is appropriate if they differ from those identified in animal models. However, it should be stressed that the metabolite(s) should be present in at least some minimal level (quantification??) in man to justify the expense and time of their re-testing in animal models. The rationale and justification for the chosen plan of action will need to be detailed.